

# **PCT**

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference  Ladner 7C-P	FOR FURTHER ACTION	CTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)							
International application No. PCT/US92/01501	International filing date (day/n 28.02.92	nonth/year)	Priority date (day/month/year) 01.03.91						
International Patent Classification (IPC) C12N15/15	or national classification and l	PC	·						
Applicant Protein Engineering Corporation et al									
<ol> <li>This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</li> <li>This REPORT consists of a total of sheets.</li> <li>This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings amended</li> </ol>									
during international preliminary examination and/or containing rectifications made before this Authority.  These annexes consist of a total of sheets.									
3. This report contains indications and corresponding pages relating to the following items:  I									
Date of submission of the demand	Date	of completion	of this report						
24.09.92		2 1. 06, 93							
Name and mailing address of the IPEA/ European Patent Office, Erhardts W-8000 Munich 2 Tel. (+49-89) 2399-0, Tx: 523656 Fax: (+49-89) 2399-4465	trasse 27	orized officer	J. Espen						

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US 92/01501

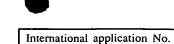
I. Ba	sis of the report								
1. This report has been drawn up on the basis of:									
χ the international application as originally filed.									
	the description	, pages	, as originally filed,						
		pages	, filed with the demand,						
		pages	, filed with the letter of,						
		pages	, filed with the letter of,						
	the claims,	No	, as originally filed,						
		No	, as amended under Article 19,						
		No	, filed with the demand,						
		No	, filed with the letter of,						
		No	, filed with the letter of,						
	the drawings,	sheets/fig.	, as originally filed,						
		sheets/fig.	, filed with the demand,						
		sheets/fig.	, filed with the letter of,						
		sheets/fig.	, filed with the letter of,						
3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box.  4. Additional observations, if necessary:									
II. Prid	ority								
1. This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:  copy of the earlier application whose priority has been claimed.									
	translation of the earlier application whose priority has been claimed.								
2. This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.									
Thus for		port, the international filing	date indicated above is considered to be the relevant date.						



International application No.

INTERNATIONAL PRELIMIN  Reasoned statement under Article 3	PCT/US 92/01501 and industrial applicability;			
citations and explanations support	ing such statement			
STATEMENT				
Novelty (N)	Claims			
	Claims			NO
Inventive Step (IS)	Claims	01 - 13		YES
	Claims			NO
		01 - 13		
Industrial Applicability (IA)	Claims Claims			310
	Ciamins			
Please, see separate	e sheet.			
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#### VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The International Preliminary Examining Authority has to issue a warning concerning a lack of unity of the present International Application (Rule 13, PCT).

The present application may be subdivided in the following groups of inventions:

- 1) inhibitors of human neutrophil elastase derived from BPTI or ITI D1 (Claims 1 and 3, respectively).
- 2) inhibitors of human cathepsin G derived from BPTI (Claim 2).
- 3) inhibitors of human neutrophil elastase consisting of derivatized peptides (Claims 7 11).

Form PCT/IPEA/409 (sixth sheet) (July 1992)





### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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VIII. Certain observations on the international application	ation
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The following observations on the claims of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The claims should be clear by themselves. However, Claims 1-2 contain internal denominations (EPi N..., Epi C...) meaningless for the person skilled in the art.



The present International Application relates to muteins of bovine pancreatic trypsin inhibitor (BPTI), inter-alpha-trypsinininhibitor-D1 (ITI-D1) and other Kunitz domain-type inhibitors which have a high affinity for elastase and cathepsin G.

Furthermore, the present application also relates to derivatized peptides which bind elastase or cathepsin G, and more particularly to elastase-binding polypeptide (EpiNe) type human neutrophil elastase (hNE) inhibitors.

Said inhibitors may be grouped into Class I, II, and III

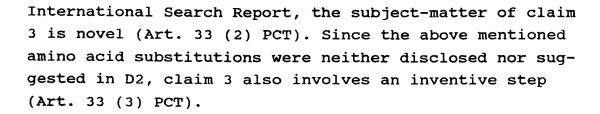
2). The subject-matter of claim 1 relates to BPTI muteins having amino acid substitutions around the P1 region. With respect to claim 1, the closest prior art document is EP-A-0 307 592 (D1) which discloses BPTI variants. Since the specific amino acid combinations of the EpiNe... claimed in claim 1 and shown in Tables 207-208 of the present application are neither described nor suggested in D1, the subject-matter of claim 1 is novel (Art. 33 (2) PCT) and also involves an inventive step (Art. 33 (3) PCT).

inhibitors (Fig. 8, 9, and 12 respectively).

The above comment also applies to claim 2, the subject-matter of which are inhibitors of human cathepsin G having amino acid (a.a.) substitutions around the P1 region (a.a. 15-19 and a.a. 39-42) of BPTI.

Claim 3 refers to inter-alpha-trypsinhibitor (ITI-D1) muteins. With respect to claim 3, the closest prior art document is EP-A-0 041 508 (D2).

Claim 3 differs from D2 in that amino acid substitutions in ITI (numbering according to D2) are disclosed for example in positions 22, 23, 25, 37, 39, and 40. Having regard to the documents cited in the



Claims 7-12 relate to derivatized peptides which are inhibitors of human neutrophil elastase.

With respect to said claims the closest prior art document is  $EP_7\lambda$ -0 195 212 (D3).

It appears that D3 neither discloses nor suggests the subject-matter of said claims, and, therefore, said claims seem to meet the requirements of Art. 33 (2) and (3) EPC.

The industrial applicability of claims 1-13 is acknowledged (Art. 33 (4) PCT).